of Boss, et al. (U.S.Patent No. 4,816,397) (hereinafter "Boss"). The Examiner characterizes Goodman as teaching the production of plants comprising cells that contain nucleotide sequences that encode biologically functional mammalian proteins and suggesting that multimeric immunoglobulins can be produced through the use of transgenic plants. The Examiner admits that Goodman does not specifically teach a plant comprised of plant cells containing nucleotide sequences encoding biologically functional multimeric proteins. The Examiner characterizes Boss as teaching the production of multimeric immunoglobulins through the use of recombinant host cell. On the basis of those characterizations, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce plants comprising cells that contain nucleotide sequences encoding mammalian peptides as taught by Goodman and to modify these plants by incorporating the nucleotide sequences encoding multimeric immunoglobulin molecules as taught by Boss and suggested by Goodman. Applicants respectfully argue against this rejection for the reason set forth below.

Independent claims 21 and 39 provide a plant that comprises plant cells containing nucleotide sequences encoding one or more biologically functional (glycopeptide-claim 39) multimeric proteins not normally produced by the plant and biologically functional multimeric proteins encoded by those nucleotide sequences. Claims 22-31 depend from claim 21 and claims 40-42 depend from claim 39. It can thus be seen that the invention requires both the presence of encoding nucleotide sequences and biologically active products of such expression. In other words, the invention requires not only expression of the multimeric protein (typically as monomers), but also correct post expression processing so as to produce a biologically active protein.

As admitted by the Examiner, Goodman can be viewed as teaching the expression of non-multimeric physiologically active mammalian proteins in plant cells but not biologically active multimeric proteins. That portion of the specification relied upon by the Examiner to support the assertion that Goodman suggests the production of immunoglobulins is nothing more than an invitation to experiment. The Examiner's attention is drawn in this regard particularly to lines 20-23 of column 3 of Goodman. [N.B. Applicants could find no mention of immunoglobulins at column 1 lines 21-23 as indicated by the Examiner.]

> "Structural genes of interest include α-, β- and γ-interferons, immunoglobulins, with the structural genes coding for the light and heavy chains and desirably assembly occurring in the plant cell, lymphokines,..."

The use of the phrase "desirably assembly occurring" clearly indicates the speculative nature of immunoglobulin expression in plant cells and indicates that correct post expression assembly of complex multimeric proteins such as immunoglobulin is unknown and a mere desire or hope at best. Such explicit speculation cannot support an obviousness-type rejection.

Boss cannot be viewed as supplying the missing elements (namely that plants have the capacity and ability to process non-naturally multimeric expression products into biologically functional multimeric proteins)necessary to lead one of ordinary skill in the art to the presently claimed invention. Indeed, Boss never so much as mentions plants whatsoever let alone the expression and processing of functional multimeric proteins in plant cells. The word "plant" never appears in Boss. The only transformed host cells specifically mentioned by Boss are

bacteria. It is noteworthy in this regard, that Goodman actually cautions the skilled worker against extrapolating from bacteria to other systems. Set forth below are lines 21-38 of column 1 of Goodman.

> "Bacteria, such as *E. coli*, *B. subtilis*, or the like, fungi, such as yeast, Candida, filamentous fungi, or the like, offer economic opportunities to produce a wide variety of peptides. However, because of the substantial difference in the nature of the unicellular microorganisms and mammalian cells, the folding and processing in a mammalian cell appears to be substantially different from these lower order organisms. Therefore, the products which are obtained from the unicellular microorganisms may not have been properly processed or folded so as to realize a substantial proportion or all of the physiological activity of the naturally occurring peptide obtained from a native host."

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine Boss and Goodman where the authors of that art themselves expressly teach against such combination.

In light of the above, Applicants respectfully submit that the Examiner has not established a *prima facie* of obviousness to support the rejection of claims 21-31 and 39-42 under 35 U.S.C. § 103(a) and they respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 101

The Examiner has provisionally rejected claim 1 under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of copending Application Nos. 08/642,406 and 09/199,534. Applicants respectfully request that the question of provisional double patenting be held in abeyance until claims are allowed in either

the instant application or the application serving as the basis for the double patenting rejection.

Rejections Under the Judicially Created Doctrine of Non-Statutory Double Patenting

The Examiner has rejected claims 1 and 21-28 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11 of U.S. Patent No. 5,639,947. Enclosed herewith is a terminal disclaimer disclaiming the term of any claims issuing in the instant application beyond the term of U.S. Patent No. 5,639,947.

Information Disclosure Statement

In recognition of their continuing duty to disclose pursuant to 37 CFR 1.56, Applicants hereby request entry of the Information Disclosure Statement filed in prior Application Serial No. 08/642,406, pursuant to 37 CFR §1.98(d).

Applicants understand that the interpretation given to each reference may differ from one individual to another. The PTO is therefore encouraged to independently examine the disclosed references. While the references provided in this Information Disclosure Statement may be material pursuant to 37 CFR 1.56, it shall not be construed to be an admission that the cited information is, or is considered to be, material to patentability unless specifically designated as such.

Applicants are filing the present statement pursuant to 37 CFR 1.97 (c), and therefore is accompanied by a check in the amount of $240.00 as payment of the fee set forth in 37 CFR §1.17 (p).

Also, in accordance with 37 CFR 1.97 (g), the filing of this Information Disclosure Statement shall not be construed to mean

that a search has been made or, that if made, any search was complete or exhaustive, or that no other material information as defined in 37 CFR 1.56 exists.

SUMMARY

In light of the comments above, Applicants respectively submit that the claims are in a condition of allowance. An early notification to that effect is hereby earnestly solicited.

Respectfully submitted,

9-9-99
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